antiplatelet treatment reduces the risk of non-fatal vascular events and, to a lesser extent, vascular death.

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Secondary prevention of vascular disease by prolonged antiplatelet treatment

ANTIPLATELET TRIALISTS' COLLABORATION

Abstract

Thirty one randomised trials of antiplatelet treatment for patients with a history of transient ischaemic attack, occlusive stroke, unstable angina, or myocardial infarction were identified. Six were still in progress, and the results of the remaining 25 were reviewed. They included a total of some 29 000 patients, 3000 of whom had died. Overall, allocation to antiplatelet treatment had no apparent effect on non-vascular mortality but reduced vascular mortality by 15% (SD 4%) and non-fatal vascular events (stroke or myocardial infarction) by 30% (4%). This suggested that with good compliance these treatments might reduce vascular mortality by about one sixth, other vascular events by about a third, and total vascular events by about a quarter. There was no significant difference between the effects of the different types of antiplatelet treatment tested (300-325 mg aspirin daily, higher aspirin doses, sulphinpyrazone, or high dose aspirin with dipyridamole), nor between the effects in patients with histories of cerebral or cardiac disease. Thus antiplatelet treatment can reduce the incidence of serious vascular events by about a quarter among a wide range of patients at particular risk of occlusive vascular disease. The balance of risk and benefit, however, might be different for "primary" prevention among people at low absolute risk of occlusive disease if antiplatelet treatment produced even a small increase in the incidence of cerebral haemorrhage.

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Introduction

Patients with a history of myocardial infarction, stroke, transient ischaemic attack, or unstable angina are at particular risk of vascular death or of a further cardiac or cerebral event. To discover whether this risk can be reduced many randomised clinical trials of various types of antiplatelet treatment have been conducted (table I).[1-36] Such treatment need not be particularly expensive or toxic, so that even risk reductions that were only moderate—for example, altering 16% into 12% recurrences within two years—might be well worth knowing about when considering how to manage an individual patient.

Though such risk reductions might be of some practical relevance,

however, they are surprisingly easy to miss, even in some of the largest currently available clinical trials. If, for example, such an effect exists then even if 2000 patients were randomised (1000 treated, 1000 control) there would be an even chance of getting a false negative result—that is, of failing to achieve convincing ($2p<0{\cdot}01$) levels of statistical significance. If, however, several different antiplatelet trials are considered then their results may usefully reinforce each other, even though the real risk reductions in different trials may be somewhat different.

An overview has therefore been attempted of the results of all randomised trials of prolonged treatment with drugs whose principal purpose is inhibition of platelet aggregation. Such overviews have two main purposes. Firstly and most obviously, they include far larger numbers of patients than individual trials do and hence yield results that are far less subject to random error. Secondly, they avoid the substantial systematic bias that may be engendered when dozens of related trials have been conducted and just a few become well known, for trials may tend to become well known partly because their results are unusually promising (or unusually unpromising). The methods used for this overview never compared patients in one trial directly with patients in another (for not only might the patients have been different but so too might the treatments, durations of treatment, quality of follow up, and end point definitions). Instead, the methods compared only like with like within one trial and did not implicitly assume that the sizes of any risk reductions in different trials must be similar.

Materials and methods

Relevant randomised trials were identified by computer aided search (Medline), by conversation with colleagues (particularly those who had coordinated such studies), by scrutiny of the reference lists of trials and review articles, and by inquiry of various manufacturers of antiplatelet agents. Six trials were still in progress and results were not expected to be available for some time. This review is of the remaining 25 trials (table I),[1-36] which included some 29 000 patients with a history of myocardial infarction, unstable angina, stroke, or transient ischaemic attack. For these trials "intention to treat" analyses of outcome by allocated treatment could be used. The aim was to review the apparent effects of treatment on non-fatal stroke—that is, stroke with survival to the end of the scheduled treatment

TABLE I—*Structure of randomised trials of antiplatelet treatment in stroke, transient ischaemic attack, myocardial infarction, or unstable angina*

Name of trial and principal investigator(s) or sources(s) of data	Type of patient	Months of delay	Total daily drug dosage (mg)	Proportion compliant at 1 year	Approximate duration of treatment (years)	Patients: No randomised	Patients: No (%) known to have had any event (that is, vascular death or non-fatal myocardial infarction or stroke)
Completed trials in patients with cerebrovascular disorders							
ESPS (European stroke prevention study; Lowenthal)	Transient ischaemic attack, reversible ischaemic neurological deficit, atherothrombotic stroke	0-3	975 aspirin + 225 dipyridamole *v* nil	0·8	2	2500	446 (18)
UK-TIA (United Kingdom transient ischaemic attack aspirin trial; Warlow, Peto)	Transient ischaemic attack, amaurosis fugax, minor stroke (12 tumours excluded)	0-3	1200 aspirin, 300 aspirin, nil	0·85	4	2448 (13 later excluded)	552 (23)
ACCSG (American-Canadian Cooperative Study Group; Fields)	Carotid transient ischaemic attack	0-3	1300 aspirin + 300 dipyridamole *v* 1300 aspirin		4	890	169 (19)
AICLA (accidents ischémiques cérébraux liés à l'athérosclérose; Bousser, Eschwege, Thibult)	Transient ischaemic attack, atherothrombotic stroke (severe deficit excluded)	0-12	990 aspirin + 225 dipyridamole, 990 aspirin, nil	0·9	3	604	109 (18)
CCSG (Canadian Cooperative Study Group; Barnett, Gent)	Transient ischaemic attack, amaurosis fugax, minor stroke	0-3	1300 aspirin, 800 sulphinpyrazone, both, nil	0·9	2	585	131 (22)
Swedish stroke (Swedish cooperative study; Britton, Helmers, Samuelsson)	Cerebral infarct (transient ischaemic attack excluded)	1	1500 aspirin *v* nil	0·7	2	505	115 (23)
McMaster (Gent)	Cerebral infarct (transient ischaemic attack excluded)	0-4	600 sulphinpyrazone *v* nil	0·8	2	447	106 (24)
Toulouse (Guiraud-Chaumeil, Loria)	Transient ischaemic attack or minor stroke (carotid endarterectomy excluded)	0-3	900 aspirin + 150 dipyridamole, 900 aspirin, nil*	0·8	3	440	41 (9)
Tohgi	Transient ischaemic attack	0-3	200 ticlopidine *v* 500 aspirin	0·5	1	340	23 (7)
AITIA (aspirin in transient ischaemic attacks; Fields, Lemak)	Hemispheric transient ischaemic attack, amaurosis fugax	0-3	1300 aspirin *v* nil	0·8	1	303	61 (20)
Toronto (Blakely)	Thrombotic stroke	?	800 sulphinpyrazone *v* nil	0·5	3	290	67 (23)
DCS (Danish cooperative study; Sorensen)	Transient ischaemic attack, amaurosis fugax (severe deficit excluded)	0-1	1000 aspirin *v* nil	0·9	2	203	49 (24)
Stoke (Acheson)	Stroke, transient ischaemic attack	0-60	400-800 dipyridamole *v* nil	0·8	2	169	43 (25)
Tennessee (Robertson)	Transient ischaemic attack, minor stroke	0-2	800 sulphinpyrazone *v* nil	0·7	6	148	46 (31)
ATIAIS (Anturan transient ischaemic attack Italian study)	Transient ischaemic attack age ≤70	0-1	800 sulphinpyrazone *v* 1000 aspirin	?	1	124	8 (6)
German TIA (German transient ischaemic attack; Reuther, Dorndorf)	Transient ischaemic attack, amaurosis fugax (no carotid stenosis)	0-3	1500 aspirin *v* nil	0·8	2	60	5 (8)
Small, old suloctidil trials (unpublished; A Lowenthal, personal communication)	?	?	Sulphinpyrazone *v* nil	?	?	Few dozen per trial?	?
Ongoing trials in patients with cerebrovascular disorders							
Harker	Transient ischaemic attack, stroke after carotid endarterectomy	?	225 dipyridamole + 975 aspirin *v* dipyridamole		In progress	Results not yet available	
TASS (North American ticlopidine-aspirin study; Hass)	Transient ischaemic attack or minor ischaemic stroke	0-1	Ticlopidine 400 *v* aspirin 1300 daily	?	5	3000?	Not known. In progress
CATS (Canadian-American ticlopidine study; Gent)	Thromboembolic stroke	0-4	500 ticlopidine *v* nil	?	3	1072	In progress
TIA + CE (transient ischaemic attack + carotid endarterectomy; Danish low dose study; Boysen *et al*)	Carotid surgery after transient ischaemic attack, stroke	0-1	50-70 aspirin *v* nil	?	Still open	224	20 (9)
3 Swedish low dose trials (Rosen, Wallentin, Elwin)	Transient ischaemic attack, stroke, angina	?	75 aspirin *v* nil	?	?	?	?
Trials in patients with myocardial infarction							
AMIS (Aspirin Myocardial Infarction Study Group)	Myocardial infarct age 30-69, no surgery	2-60	1000 aspirin *v* nil	0·9	3	4524	874 (19)
PARIS-II (Second Persantin-Aspirin Reinfarction Study Group)	Myocardial infarct age <75	1-4	972 aspirin + 225 dipyridamole *v* nil	0·7	2	3128	438 (14)
PARIS-I (First Persantin-Aspirin Reinfarction Study Group)	Myocardial infarct age <75	2-60	972 aspirin + 225 dipyridamole, 972 aspirin, nil	0·7	3-4	2026	380 (19)
Cardiff-II (MRC epidemiology unit; Elwood, Sweetnam)	Myocardial infarct	0-1	900 aspirin *v* nil	0·7	1	1682	314 (19)
ART (Anturan reinfarction trial; Sherry)	Myocardial infarct	1	800 sulphinpyrazone *v* nil	0·8	1·3	1620	270 (17)
CDP-A (Coronary Drug Project Aspirin Research Group)	Myocardial infarct	Most >60	972 aspirin *v* nil	0·8	2	1529	179 (12)
GDR (Micristin study; Vogel)	Myocardial infarct (bad failure, stroke excluded)	1-2	1500 aspirin *v* nil	0·8	2	1340	150 (11)
Cardiff-I (MRC epidemiological unit; Elwood, Sweetnam)	Myocardial infarct age <65	0-6	300 aspirin *v* nil	0·7?	1	1239	136 (11)
ARIS (Anturan reinfarction Italian study; Cortellaro)	Myocardial infarct age <70	0-1	800 sulphinpyrazone *v* nil	0·8	1·7	727	101 (14)
GAMIS ((West) German-Austrian myocardial infarction study; Breddin)	Myocardial infarct age <70, diastolic blood pressure >110 mm Hg	1	1500 aspirin *v* nil (*v* anticoagulants†)	0·8	2	626	96 (15)
Trials in patients with unstable angina							
VA (main + pilot) (Veterans Administration study; Lewis)	Unstable angina (women, recent myocardial infarction excluded)	0	324 aspirin *v* nil	0·9	0·25	1388 (1338 + 50)	125 (9)
Canadian unstable angina study (McMaster; Cairns, Gent)	Unstable angina (recent myocardial infarction excluded)	0	1300 aspirin , 800 sulphinpyrazone, both, nil	0·8	2	555	75 (14)

*Co-dergocrine mesylate also given to patients in these groups.
†A third randomised group anticoagulated with phenprocoumon not included in present overview.

period—on non-fatal myocardial infarction, on vascular death, and on non-vascular death. Table I shows that the trials were very heterogeneous, including a range of ages, a range of different diseases, a range of treatments (the one most extensively tested being aspirin), and so on. Hence the statistical method used was one that did not unjustifiably assume homogeneity. Firstly, for each separate trial some measure of the difference in outcome between treated and control was calculated that would differ only randomly from zero if treatment did nothing within that one particular trial. Next, all these separate measures (one per trial) were summed to see whether their grand total differed significantly from zero (fig 1). If treatment did

Trial 1	Difference 1 (treated 1 *v* control 1)
Trial 2	Difference 2 (treated 2 *v* control 2)
Trial 3	Difference 3 (treated 3 *v* control 3)
Grand total	Difference 1 + difference 2 + difference 3

NB (a) Test of whether grand total differs significantly from zero entails only comparison of like with like within each separate trial.

(b) Variance of grand total may be calculated simply by adding separate variances of each separate difference.

FIG 1—Principle of unbiased combination of information from different trials.

nothing in any trial then each separate measure would differ only randomly from zero and so would the grand total. Such statistical arguments do not compare patients in one trial directly with patients in another, nor do they implicitly assume that any non-zero treatment effects in different trials must be of similar size.

Hypothetical data:
N = 1000 subjects
p = Proportion allocated active treatment = 0·5
D = Total number dead = 65

	Active treatment group	Control group	
Died	25*	40	65 =D
Survived			935
	500	500	1000 =N

*O–E Calculated only for active treatment group :
O=25, E=32·5 (that is, pD); difference (O–E) = –7·5.

NB (a) In evenly balanced study such as this example O–E of –7·5 corresponds to apparent prevention not of 7·5 deaths but of 15 deaths.

(b) Variance of O–E may be calculated by standard statistical formula E (1–p) (N–D)/(N–1).

FIG 2—Calculation of observed minus expected (O–E).

STATISTICAL METHODS

In an overview of many trials a particularly appropriate measure of the result in each separate trial with respect to some particular type of "failure" is provided by the standard calculation of observed minus expected numbers of such failures in the actively treated group alone. The calculation tends to give a negative result if treatment works, and in an evenly balanced trial it is equal in size to about half the number of patients protected (fig 2). For example, in an evenly balanced trial an observed minus expected figure of –40 would suggest that treatment had saved about 80 patients from failure during the study (fig 2). Reasons for using O-E in adding up information from many trials were given by Yusuf *et al*[37] along with statistical details of variance calculations and of how to use the grand total and its variance (V). These provide a theoretically optimal test of whether any statistically significant treatment effect exists (via calculation of z, the number of its standard deviations (S) by which the grand total (GT) differs from zero). They also provide a useful estimate of the percentage reduction in the odds of

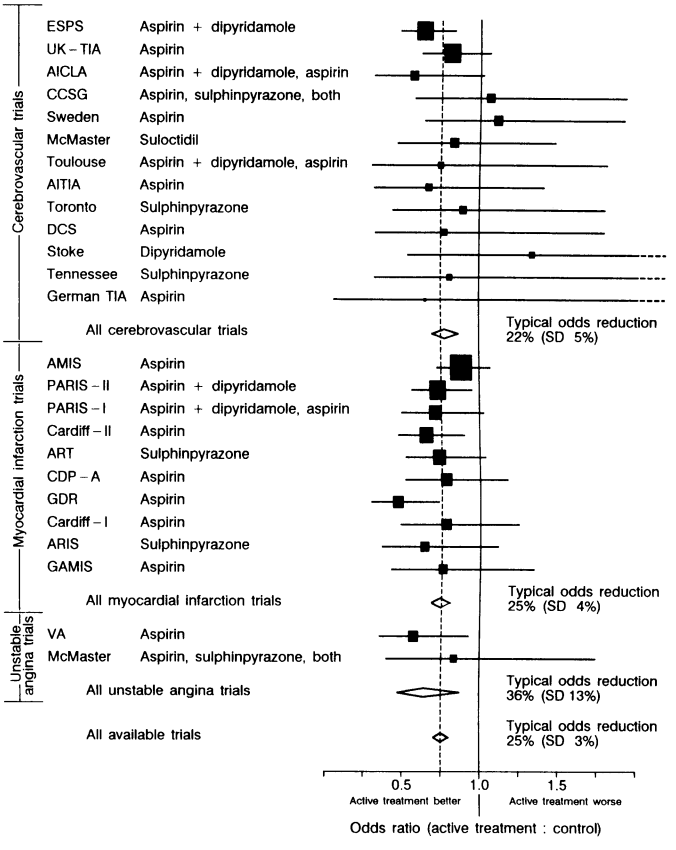

FIG 3—Odds ratios (active treatment:control) for first stroke, myocardial infarction, or vascular death during scheduled treatment period in completed antiplatelet trials. —■—=Trial results and 99% confidence intervals (area of ■ proportional to amount of information contributed). ◇=Overview results and 95% confidence intervals. Dashed vertical line represents odds ratio of 0·75 suggested by overview of all trial results. Solid vertical line represents odds ratio of unity (no treatment effect).

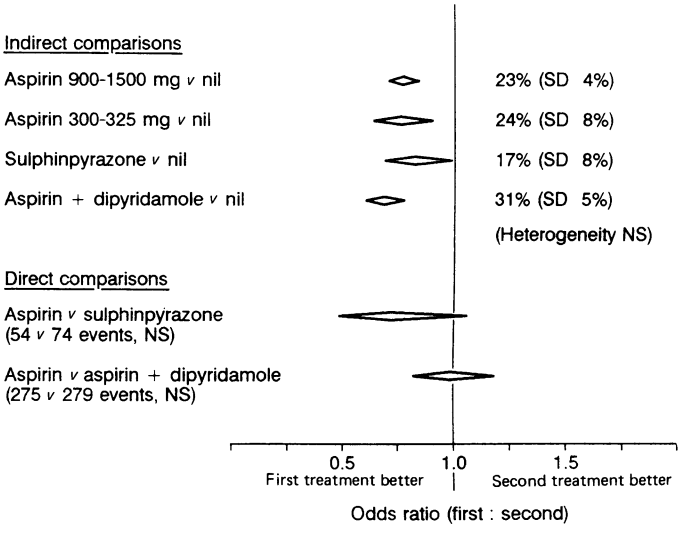

FIG 4—Direct and indirect comparisons between reductions in new vascular event rates with different antiplatelet agents. ◇=95% Confidence intervals for typical odds ratios.

failure that is typical in such trials and of the standard deviation (SD) of this typical odds reduction. (The odds ratio that is "typical" in a series of heterogeneous trials may be estimated[37] by exp(GT/V) with approximate 95% confidence limits exp(GT/V-1·96/S) and exp(GT/V+1·96/S). The percentage, P, by which this differs from unity has an SD of approximately P/z.) Again, calculation of such an estimate of risk reduction does not implicitly assume that the true risk reductions in all trials are the same. The typical odds reduction merely provides a useful indication of the risk reduction that is typical in a heterogeneous collection of real clinical trial results.

Two tailed p values (2p) were used in the primary analysis and 1 tailed p values (1p) thereafter. To help allow for multiple hypothesis testing 99% confidence intervals were plotted for individual trial results (fig 3), though 95% intervals were plotted for overview results (figs 3, 4).

In a small, uninformative trial the variance of observed minus expected would be small, whereas in a large, reliable trial the variance of observed minus expected would be large. (For example, in a very small trial where only one person died the variance of observed minus expected might be about 0·2, whereas in a large trial where, say, 400 patients died the variance of observed minus expected might be nearly 100.) To give greater emphasis to the better studies the areas of the squares used to plot different trial results (fig 3) were made proportional to the variance of observed minus expected, for this is a measure of the statistical information content of each trial. Hence the width of each square (fig 3) is proportional to S, the standard deviation of observed minus expected (using the arbitrary convention width=0·01 S).

Results

Table I lists the trials that were identified; the main results were obtained from the principal investigators in most cases. For some trials the data obtained differed slightly from the data originally published. In general this was because considerable efforts were made to seek complete follow up data on all randomised subjects, including not only events while treatment continued but also events before the scheduled end of trial treatment (which was on a common date for all patients in some trials, at a fixed interval after randomisation in others, and at a combination of these two dates in two trials[33 36]). In some cases this included review of records that had been collected by the trialists but not used, and in others it entailed collection by the trialists of additional records. In neurological trials many patients suffered myocardial infarction and more deaths were attributed to heart disease than to stroke. Conversely, in the heart disease trials many patients suffered a stroke. As antiplatelet treatment might affect either condition, the primary analysis was of the effect of allocated treatment on the odds of suffering at least one important vascular event. Important vascular events were defined as excluding transient ischaemic attacks, angina, and "possible" myocardial infarctions but generally including "definite" strokes that caused symptoms that persisted for at least 24 hours and non-fatal myocardial infarctions that were classified as "probable" or "definite," together with all deaths that might have been vascular or haemorrhagic—that is, ICD (9th revision) codes 390-459, 530-535, 578, and 797-799. There were, of course, slight differences between different studies in how vascular events were categorised, but because retrospective reclassification of many vascular events would have been impracticable the definitions preferred by the original investigators in each study were generally retained. The heterogeneity that this entailed does not bias or invalidate the main overview results (see below).

NON-VASCULAR MORTALITY

When this collaboration was initiated the fundamental purpose was to assess the main effects of treatment on various types of fatal and non-fatal vascular events (stroke, myocardial infarction, and vascular death). Hence deaths were classified merely as "vascular"—that is, possibly or definitely vascular or haemorrhagic—or "non-vascular," with no further subdivision of the non-vascular deaths. If antiplatelet treatment does have some unanticipated protective or adverse effect that might have been disclosed by a cause specific analysis of the non-vascular deaths, a crude overall analysis of the available data on total non-vascular mortality might well yield an uninformatively non-significant result (as, of course, might analysis of total all cause mortality, in which any effects on particular non-vascular causes might be swamped by any effects on the much commoner vascular causes). Despite these limitations table II presents the analyses of total non-vascular mortality. Overall there was a very slight tendency for there to be fewer non-vascular deaths among patients allocated to treatment than would have been expected if in each separate study the prognosis of the treated patients had been identical with that of their matched controls, but the difference was small (total observed among patients allocated to treatment 280; total expected 287·3 (table II)) and wholly non-significant. As originally planned, these non-vascular deaths were excluded from all subsequent analyses of vascular event rates; nevertheless, as they indicated little or no effect of treatment their exclusion or inclusion would have had little or no effect on the main conclusions.

OVERALL ANALYSIS OF ALL THREE TYPES OF VASCULAR EVENT

Table III presents the main results from each trial in terms of the numbers of patients suffering important vascular events—that is, stroke or myocardial infarction or vascular death (separate analyses for these three conditions are given below). In 22 of the 25 trials these main results favoured antiplatelet treatment—that is, the number of patients allocated to treatment who were observed to suffer at least one such event was smaller than the number who would have been expected to do so if the event rates among controls and treated patients had been similar. Moreover, even in the remaining three trials the statistic observed minus expected was only slightly positive, whereas for many of the 22 trials whose results favoured treatment the statistic observed minus expected was strikingly negative, so that the grand total of all 25 observed minus expected values in table III (which would have differed only randomly from zero if treatment had done nothing in any trial) was −272·0. This is much more extremely negative than could reasonably be accounted for by chance. (The variance of this grand total was 954·6; the standard deviation is the square root of 954·6—that is, 30·9—so the grand total is 8·8 standard deviations in favour of treatment ($2p<0·0001$).)

A crude way of translating the grand total of −272·0 from statistical into medical terms is simply to double it and conclude that treatment in these trials appeared to have protected about 500 or 600 patients against such an event. A more accurate way of using the grand total is suggested in the statistical methods section, which indicates that in these trials the typical reduction in the odds of suffering a vascular event was 25% (SD 3%). (Note that because of the approximate cancellation of two small correction factors that point in opposite directions, if allocation to active treatment can reduce the odds of suffering a vascular event by about a quarter then actual use of active treatment can reduce the probability of suffering a vascular event by about a quarter.)

The key point, however, is not the statistical details but the statistical principles, which do not entail any unjustifiable medical assumptions. It is not assumed that the effects in patients with a history of cerebral and cardiac events were necessarily the same size (though they did not appear to be greatly different (table III)), nor is it assumed that different antiplatelet treatments were necessarily equivalent, and nor is it assumed that the results from each trial were precisely "correct"; indeed, in addition to any intended differences between studies in the definitions of what constituted a stroke, myocardial infarction, or vascular death, numerous other omissions and errors must have occurred in the determination of who suffered a vascular event and who did not. All that is assumed is that these potentially substantial sources of error in the results for individual patients were largely random in their effects on the treatment comparisons, so that within each trial the comparison of treatment with control was not subject to any substantial bias and that likewise no substantial bias was introduced by the choice of which randomised trials to study. (In this context "substantial" bias means bias that might plausibly account for a substantial proportion of the 25% risk reduction that the trial results collectively suggested.)

Table III suggests a general consistency of the different trial results. Figure 3 displays the results from each separate trial for important vascular events together with various overviews of these trial results. The result for each trial is plotted in terms of the odds ratio (treated *v* control) and 99% confidence interval, using black squares whose areas indicate the amount of information contributed by each trial. Overview results are presented with their 95% confidence intervals and corresponding typical percentage odds reductions and standard deviations. The odds ratio of 0·75 suggested by the overview of all the trial results (dashed vertical line) indicates a reduction of 25% (SD 3%; table III) in the odds of suffering an important vascular event. Table III gives details of the underlying calculations. For all but five[1 23 26 29 36] of the trials the odds ratio of unity (vertical solid line; no treatment effect) is crossed by the confidence interval for that trial, indicating that, taken separately, those trials did not provide clear evidence of benefit. For almost all trials, however, the point estimates are somewhat to the left of unity, suggesting some benefit, and in the overviews these separate tendencies reinforce each other to produce overwhelmingly definite evidence of benefit.

In figure 3 the confidence interval for each separate trial reaches or overlaps the 25% reduction in the odds of failure suggested by the overview of all completed trials (dashed vertical line). This suggests that no trial yielded a benefit clearly significantly better or clearly significantly worse than 25%. Indeed, though the separate trials do not all indicate exactly the same risk reduction, the amount of scatter is no greater than might be expected by chance if the true risk reduction in each study was exactly 25%.

(Formally, the statistical test for heterogeneity (table III) yielded a non-significant result.) This lack of significant heterogeneity of benefit is, however, of limited relevance, partly because such tests are surprisingly insensitive to any real differences that may exist between different studies, but chiefly because whatever result a formal heterogeneity test might yield it is not reasonable (and not necessary for the overview) to suppose the true risk reductions in all trials to be identical.

SUBDIVISIONS OF MAIN ANALYSIS

The main analysis entailed review of all randomised trials (irrespective of whether the criterion for entry was a history of cerebrovascular disease, of myocardial infarction, or of unstable angina) of the effects on any important vascular events (irrespective of whether the criterion for failure was non-fatal stroke, non-fatal myocardial infarction, or vascular death) of any type of antiplatelet treatment (irrespective of whether the agent tested was high dose aspirin, medium dose aspirin, aspirin with dipyridamole, sulphinpyrazone, etc). Subdivisions of this main analysis will now be presented with respect to the type of prior disease, the type of outcome, and the type of treatment.

Table III and figure 3 were subdivided with respect to the type of prior disease, but there was no significant heterogeneity between the treatment effects achieved in the trials among patients with a history of cerebrovascular disease (22% (SD 5%)), myocardial infarction (25% (4%)), and unstable angina (36% (13%)). All differed by less than one standard deviation from the 25% reduction seen in the main analysis. The proportional risk reduction in patients with unstable angina appeared somewhat greater than that in other categories of patient, and the difference may well have been real: nevertheless, it was not statistically significant, and evidence other than that reviewed in this paper will be needed to resolve this issue.

Differences between different measures of outcome

Tables IV and V give the results separately for non-fatal myocardial infarction and non-fatal stroke. In both cases there were risk reductions of about 30%, suggesting that use of antiplatelet treatment—that is, with 100% compliance—might reduce the odds of suffering such non-fatal events by about one third. These risk reductions were both so significantly and substantially different from zero that the unavailability of full data from the few trials that were still in progress was unlikely to be important. For most of the non-fatal strokes in the cerebrovascular trials information was reviewed on whether the strokes were bad enough to leave substantial residual disability (Rankin grade 3 or more) six months after the event (data not shown). This review suggested that the percentage reduction conferred by antiplatelet treatment was somewhat greater for disabling than for non-disabling stroke, but from some cerebral and all cardiac trials such data were not available for review.

With regard to vascular death (table VI) the effects of treatment were again highly significant (3·6 standard deviations from zero; 2p=0·0003), and especially in view of the established effects of treatment on non-fatal vascular events this difference may be accepted as real. The apparent size of the risk reduction (15% (SD 4%)), however, was only about half as great as for non-fatal events, so it was particularly important to confirm the absence of any substantial sources of bias. The unavailability of data from the six trials still in progress was unlikely to be a serious source of bias because the numbers of

TABLE II—*Non-vascular deaths recorded in trials of antiplatelet treatment*

	Basic data		Statistical calculations (treatment group only)			
	Allocated antiplatelet treatment	Allocated to control group	Observed deaths (O)	Expected deaths (E)	Difference (O−E)	Variance of O−E
Completed cerebrovascular trials:						
ESPS	29/1250	50/1250	29	39·5	−10·5	19·1
UK-TIA	49/1621	36/814	49	56·6	−7·6	18·3
AICLA	11/400	6/204	11	11·3	−0·3	3·7
CCSG	12/446	2/139	12	10·7	1·3	2·5
Swedish stroke	6/253	8/252	6	7·0	−1·0	3·4
McMaster	16/222	17/225	16	16·4	−0·4	7·7
Toulouse	11/284	6/156	11	11·0	0.0	3·8
AITIA	0/153	3/150	0	1·5	−1·5	0·7
Toronto	16/143	13/147	16	14·3	1·7	6·6
DCS	4/101	2/102	4	3·0	1·0	1·5
Stoke	1/85	1/84	1	1·0	0·0	0·5
Tennessee	0/73	0/75	0	0	0	0
German TIA	0/30	0/30	0	0	0	0
All cerebrovascular trials (excluding six still in progress*)	299/8689 (3%)†		155	172·2	−17·2 (2·1 SD from zero)	67·6
Myocardial infarction trials:						
AMIS	32/2267	21/2257	32	26·6	5·4	13·1
PARIS-II	14/1563	9/1565	14	11·5	2·5	5·7
PARIS-I	24/1620	7/406	24	24·8	−0·8	4·9
Cardiff-II	5/832	4/850	5	4·4	0·6	2·2
ART	9/806	7/814	9	8·0	1·0	4·0
CDP-A	2/758	4/771	2	3·0	−1·0	1·5
GDR	17/672	19/668	17	18·0	−1·0	8·8
Cardiff-I	2/615	4/624	2	3·0	−1·0	1·5
ARIS	4/365	2/362	4	3·0	1·0	1·6
GAMIS	7/317	2/309	7	4·6	2·4	2·2
All myocardial infarction trials	195/18 441 (1%)		116	106·8	9·2 (1·4 SD from zero)	45·5
Unstable angina trials:						
VA (main+pilot)	0/687	0/701	0	0	0	0
McMaster (three groups *v* one)	3/416	0/139	3	2·2	0·8	0·6
All unstable angina trials	3/1943 (0·2%)†		3	2·2	0·8 (1·0 SD from zero)	0·6
All available trials	497/29 073 (2%)†		280	287·3	−7·3 (0·7 SD from zero; NS)	113·7

*Danish low dose aspirin, Swedish low dose aspirin (three trials), Harker dipyridamole+aspirin, Canadian ticlopidine.
†Totals for treated and control groups combined (as separate totals could not validly be compared).
NS=Not significant (2p>0·1).
Test for heterogeneity among sizes of treatment effects in 22 trials with at least some non-vascular deaths: χ^2 on 21 degrees of freedom=23·3 (NS).

vascular deaths in those trials had not become large enough for a premature halt to be likely. A marginally significant imbalance in prognostic features was recorded in only one large trial (AMIS)[22] and not in any other. Statistical correction for this imbalance would, however, alter the overall reduction in vascular mortality only slightly, improving it from 15% to 17% (table VI).

One reason why the effects of treatment appeared to be less extreme for vascular death than for the non-fatal events considered in tables IV and V is possible source of data that might be used to distinguish with reasonable statistical power between the effects of different antiplatelet agents. Another source was provided by the data from the present trials on total vascular event rates (fig 3), which may be subdivided according to the type of agent tested (table VII, fig 4). Though vascular deaths are generally more important than vascular events, the overall effect of treatment was much clearer for events than for deaths, so any important differences between the

TABLE III—*Important vascular events (first myocardial infarction, stroke, or vascular death) recorded in trials of antiplatelet treatment*

	Basic data		Statistical calculations (treatment group only)		
	Allocated antiplatelet treatment	Allocated to control group	Observed No minus expected (O−E)	Variance of O−E	p Value (one tailed)
Completed cerebrovascular trials:					
ESPS	182/1250	264/1250	−41·0	91·7	<0·0001
UK-TIA	348/1621	204/814	−19·5	95·0	0·02
AICLA	61/400	48/204	−11·2	20·0	0·01
CCSG	101/446	30/139	1·1	18·5	NS
Swedish stroke	60/253	55/252	2·4	22·3	NS
McMaster	49/222	57/225	−3·6	20·3	NS
Toulouse	24/284	17/156	−2·5	8·5	NS
AITIA	26/153	35/150	−4·8	12·2	NS
Toronto* (death only)	34/143	38/147	−1·5	13·6	NS
DCS	22/101	27/102	−2·4	9·3	NS
Stoke (excluding myocardial infarction)	24/85	19/84	2·4	8·1	NS
Tennessee (excluding myocardial infarction)	21/73	25/75	−1·7	8·0	NS
German TIA	2/30	3/30	−0·5	1·2	NS
All cerebrovascular trials (excluding six still in progress (table II))	1776/8689 (20%)‡		−82·7 (4·6 SD from zero)	328·5	0·0001 Typical odds reduction 22% (SD 5%)
Myocardial infarction trials:					
AMIS	416/2267	458/2257	−22·0	176·3	0·05
PARIS-II	189/1563	249/1565	−29·9	94·2	0·001
PARIS-I	287/1620	93/406	−16·9	49·5	0·01
Cardiff-II	128/832	186/850	−27·3	63·9	0·0003
ART	117/806	153/814	−17·3	56·3	0·01
CDP-A	79/758	100/771	−9·7	39·5	0·06
GDR	50/672	100/668	−25·2	33·3	<0·0001
Cardiff-I	60/615	76/624	−7·5	30·3	0·09
ARIS	41/365	60/362	−9·7	21·8	0·02
GAMIS	43/317	53/309	−5·6	20·4	NS
All myocardial infarction trials	2938/18 441 (16%)‡		−171·1 (7·1 SD from zero)	585·5	<0·0001 Typical odds reduction 25% (SD 4%)
Unstable angina trials:					
VA (main+pilot)	46/687	79/701	−15·9	28·5	0·001
McMaster (three groups *v* one†)	54/416	21/139	−2·2	12·2	NS
All unstable angina trials	200/1943 (10%)‡		−18·1 (2·8 SD from zero)	40·7	0·002 Typical odds reduction 36% (SD 13%)
All available trials	4914/29 073 (17%)‡		−272·0 (8·8 SD from zero)	954·6	0·0001 Typical odds reduction 25% (SD 3%)

*Data on non-fatal events unavailable.
†Analysis of this four way trial was of any antiplatelet agent (sulphinpyrazone or aspirin or both versus nil), which differed from main published analysis of two aspirin groups versus two non-aspirin groups.
‡Totals for treated and control groups combined (as separate totals could not validly be compared).
Test for heterogeneity among 25 completed trials: $\chi^2=30{\cdot}2$, df=24, NS.
Test for heterogeneity among 13 cerebrovascular trials: $\chi^2=13{\cdot}4$, df=12, NS.
Test for heterogeneity among 10 postmyocardial infarction trials: $\chi^2=14{\cdot}2$, df=9, NS.
Test for heterogeneity among two angina trials: $\chi^2=1{\cdot}2$, df=1, NS.

simply that various medical events in the weeks or months before vascular death may sometimes have resulted in withdrawal of medication from some patients who were having active trial treatment or in the start of antiplatelet treatment for some controls. Correction for this might perhaps indicate that full compliance with the allocated treatment (except where specifically contraindicated) would reduce the odds of vascular death by at least 20%, but any such estimates are subject to substantial uncertainty (see Discussion).

Differences between different antiplatelet treatments

Because of the difficulty in assessing directly the overall effects of antiplatelet treatment on mortality, with the data available there was no prospect whatever of distinguishing directly between the effects of different treatments on vascular mortality rates with any degree of reliability. Recourse must therefore be made to other types of data where the effects of antiplatelet treatment on thrombotic events might be measured with a smaller coefficient of variation. Studies of graft or shunt patency provide one

effects of different treatments would likewise be expected to be clearer for events than for deaths.

Table VII and figure 4 show that the risk reductions suggested by separate overviews of the trials of various different antiplatelet agents were 23% (SD 4%) for 900-1500 mg aspirin *v* nil, 24% (8%) for 300-325 mg aspirin *v* nil, 17% (8%) for sulphinpyrazone *v* nil, and 31% (5%) for aspirin plus dipyridamole *v* nil. The results of these indirect comparisons were not significantly heterogeneous and so provided no clear evidence that one antiplatelet agent was more effective than another. Though the average effect was somewhat greater in the trials of dipyridamole plus aspirin than in the trials of aspirin alone, this difference was not significant. In addition, there were some direct randomised comparisons between aspirin and another agent (table VII, fig 4) but these were too small to be reliable. Nevertheless, they did not suggest that any other antiplatelet regimen was better than plain aspirin. Similarly, the one direct comparison of 300 mg daily aspirin with 1200 mg also failed to yield any significant difference (UK-TIA Study Group, accompanying paper). These results are considered in more detail below.

Discussion

VALIDITY OF OVERVIEWS OF SEVERAL VERY DIFFERENT TRIALS

The assumptions inherent in overviews of several related but quite different trials have been discussed elsewhere (for example, Yusuf *et al*[37]). Briefly, it is not assumed that the patients in one trial are comparable with those in another, nor that different antiplatelet treatments have equivalent therapeutic effects, nor that the same agent must have the same size of effect in different trials. The key assumption is merely that if antiplatelet agents have any material effect on incidence of disease then the direction, though not necessarily the size, of this effect will tend to be similar in different circumstances (as long as these circumstances are not completely different—for example, use in patients with a history of recent cerebral haemorrhage). The other important assumption is that for treatments that are inexpensive and not particularly toxic a moderate therapeutic effect, too small to be detected reliably even among a few thousand people, may nevertheless be worth while if it involves something as serious as death or permanent disability.

NON-VASCULAR MORTALITY

For non-vascular deaths in this overview of antiplatelet trials the total numbers observed and expected among patients allocated active treatment were 280 and 287·3 (table II), and the corresponding numbers from a six year study of British doctors were 122 and 129·4 (Peto *et al*, accompanying paper). Thus in total there were slightly fewer non-vascular deaths than expected among people allocated active treatment (total observed 402, total expected 416·7). These findings indicate that a few years of antiplatelet treatment with such agents has little or no adverse effect on overall non-vascular mortality but do not answer the more interesting question of whether any specific non-vascular causes of death are favourably or unfavourably affected.

VASCULAR EVENTS AND VASCULAR DEATH

In contrast, a significant (2p=0·0003) reduction in vascular mortality was seen (and the reduction in all cause mortality was also significant: z=3·5, 2p=0·0003), and both of these differences would have been slightly more significant had an appropriately adjusted analysis of the AMIS trial been used (table VI). In view of the extremely significant reductions in non-fatal myocardial infarction (2p<0·0001; table IV) and non-fatal stroke (2p<0·0001; table V) that were also seen the reduction in vascular mortality among such patients can safely be accepted as real.

DIFFERENCES BETWEEN DIFFERENT TYPES OF PATIENT

The observed benefit among patients with unstable angina was somewhat greater than that in patients with a history of myocardial

TABLE IV—*Non-fatal myocardial infarctions recorded in trials of antiplatelet treatment (numbers affected but with survival to end of study)*

	Basic data		Statistical calculations (treatment group only)	
	Allocated antiplatelet treatment	Allocated to contol group	Observed No minus expected (O−E)	Variance of O−E
Completed cerebrovascular trials:				
ESPS	21/1250	35/1250	−7·0	13·7
UK-TIA	42/1621	34/814	−8·6	16·4
AICLA	4/400	9/204	−4·6	2·8
CCSG	15/446	0/139	3·6	2·7
Swedish stroke	10/253	10/252	0	4·8
McMaster	4/222	4/225	0	2·0
Toulouse	0/284	2/156	−1·3	0·5
AITIA	4/153	2/150	1·0	1·5
Toronto	?/143	?/147	—	—
DCS	2/101	8/102	−3·0	2·4
Stoke	?/85	?/84	—	—
Tennessee	?/73	?/75	—	—
German TIA	0/30	0/30	0	0
All cerebrovascular trials (excluding six still in progress (table II))	≥206/8689 (2%)*		−19·9 (2·9 SD from zero; 1p=0·002)	46·7 Typical odds reduction 35% (SD 12%)
Myocardial infarction trials:				
AMIS	175/2267	214/2257	−19·9	88·9
PARIS-II	71/1563	111/1565	−19·9	42·9
PARIS-I	120/1620	40/406	−7·9	23·6
Cardiff-II	31/832	63/850	−15·5	22·2
ART	43/806	50/814	−3·3	21·9
CDP-A	28/758	32/771	−1·7	14·4
GDR	32/672	60/668	−14·1	21·4
Cardiff-I	12/615	15/624	−1·4	6·6
ARIS	15/365	33/362	−9·1	11·2
GAMIS	11/317	16/309	−2·7	4·5
All myocardial infarction trials	1172/18 441 (6%)*		−95·6 (6·0 SD from zero; 1p<0·0001)	257·7 Typical odds reduction 31% (SD 5%)
Unstable angina trials:				
VA (main+pilot)	27/687	50/701	−11·1	18·2
McMaster (three groups *v* one)	24/416	7/139	0·8	5·5
All unstable angina trials	108/1943 (6%)*		−10·4 (2·1 SD from zero; 1p=0·02)	23·7 Typical odds reduction 35% (SD 17%)
All available trials	≥1486/29 073 (5%)*		−125·9 (7·0 SD from zero; 2p<0·0001)	328·1 Typical odds reduction 32% (SD 5%)

*Totals for treated and control groups combined (as separate totals could not validly be compared).

TABLE V—*Non-fatal strokes recorded in trials of antiplatelet treatment (numbers affected but with survival to end of study)*

	Basic data		Statistical calculations (treatment group only)	
	Allocated antiplatelet treatment	Allocated to control group	Observed No minus expected (O−E)	Variance of O−E
Completed cerebrovascular trials:				
ESPS	82/1250	127/1250	−22·5	47·9
UK-TIA	139/1621	92/814	−14·8	46·5
AICLA	32/400	27/204	−7·1	11·9
CCSG	60/446	15/139	2·8	11·9
Swedish stroke	23/253	18/252	2·5	9·4
McMaster	24/222	22/225	1·1	10·3
Toulouse	6/284	8/156	−3·0	3·1
AITIA	12/153	20/150	−4·2	7·2
Toronto	4/143	2/147	1·0	1·5
DCS	14/101	12/102	1·1	5·7
Stoke	12/85	11/84	0·4	5·0
Tennessee	10/73	6/75	2·1	3·6
German TIA	2/30	3/30	−0·5	1·2
All cerebrovascular trials (excluding six still in progress (table II))	783/8689 (9%)*		−41·0 (3·2 SD from zero; 1p=0·0005)	165·2 Typical odds reduction 22% (SD 7%)
Myocardial infarction trials:				
AMIS	27/2267	46/2257	−9·6	18·0
PARIS-II	21/1563	33/1565	−6·0	13·3
PARIS-I	19/1620	8/406	−2·6	4·3
Cardiff-II	?/832	?/850	—	—
ART	9/806	21/814	−5·9	7·4
CDP-A	9/758	8/771	0·6	4·2
GDR	6/672	14/668	−4·0	4·9
Cardiff-I	?/615	?/624	—	—
ARIS	1/365	4/362	−1·5	1·2
GAMIS	?/317	?/309	—	—
All myocardial infarction trials with data on stroke	≥226/18 441 (1%)*		−29·1 (4·0 SD from zero; 1p<0·0001)	53·3 Typical odds reduction 42% (SD 11%)
Unstable angina trials:				
VA (main+pilot)	3/687	2/701	0·5	1·3
McMaster (three groups *v* one)	3/416	1/139	0	0·8
All unstable angina trials	9/1943 (0·5%)*		0·5	2·0
All available trials with data on stroke	≥1018/29 073 (4%)*		−69·5 (4·7 SD from zero; 2p<0·0001)	220·5 Typical odds reduction 27% (SD 6%)

*Totals for treated and control groups combined (as separate totals could not validly be compared).

infarction or of cerebrovascular disease, but the difference was not clearly significant (and deletion of the unstable angina trials would not greatly affect the significance of the risk reductions in the remaining patients). Thus though antiplatelet treatment may have a somewhat greater effect in unstable angina (particularly during the first few weeks), we have no really clear evidence that it does—or, indeed, that it had a proportionally greater or less effect in any particular category of patient in these studies.

The net advantages of antiplatelet treatment may therefore hold for a wide range of types of patient with a history of occlusive vascular disease. This conclusion depends partly on the fact that several different categories of such patients have already been studied. Chiefly, however, it depends on the commonsense notion that if antiplatelet treatment averts a certain proportion of occlusive vascular events in one category of patient then though the proportion averted in another category may not be identical, it is unlikely to be vastly different—and, in particular, it is unlikely to be zero. In common parlance, there may well be differences in degree but there are unlikely to be differences in kind between the effects of treatment on a particular type of outcome (or, in statistical parlance, quantitative interactions may well exist but unanticipated qualitative interactions are unlikely[38]). For different diseases—cerebral haemorrhage, for example—the effects of antiplatelet treatment might well be exactly opposite, but the present studies show that the treatments tested are of net benefit among patients such as those actually randomised, who were thought to be at substantially increased risk of an occlusive vascular event but not at particularly increased risk of a major haemorrhagic event. Hence it might be reasonable to infer that provided that there was no special contraindication antiplatelet treatment would probably also be of net benefit for an even wider range of patients who are for some reason at particular risk of occlusive vascular disease.

Perhaps it would be possible to extrapolate too far and reach mistaken conclusions that engender inappropriate treatment. It would also, however, be possible to engender inappropriate treatment by taking too formal a view of the existing evidence and so not extrapolating far enough, thereby denying treatment to many patients who would in fact benefit. Thus the information from trials can provide guidance in the treatment of a far wider range of patients than just those studied in the trials, though the further the extrapolation the more desirable it would be to have direct evidence. So, for example, direct evidence is needed, and is currently being sought, about the value of beginning a few weeks of antiplatelet treatment immediately on admission for coronary care (ISIS[39]) and of aspirin in the "primary" prevention of disease among apparently healthy people whose absolute risks of occlusive events are low and among whom, therefore, even a small increase in serious haemorrhagic events might outweigh the expected decrease in occlusive events (Peto *et al*, accompanying paper).[40]

DIFFERENCES BETWEEN DIFFERENT DOSES OF ASPIRIN

The most convenient and least expensive type of antiplatelet agent is low dose aspirin. Unfortunately, we have little direct evidence about the antithrombotic effects of very low doses (for example, less than 100 mg/day[19 41 42]), and all the aspirin trials in this

overview that did not use 300-325 mg/day used 900-1500 mg/day. These higher doses are less convenient and more gastrotoxic than 300 mg/day (UK-TIA Study Group, accompanying paper), so they could be recommended for routine use only if there was reasonably good evidence that they were more effective. Pharmacological studies, however, suggest that cyclo-oxygenase dependent platelet aggregation is inhibited just as effectively by 300 mg of aspirin as by higher doses; indeed, some pharmacologists have suggested that doses substantially lower than 300 mg/day might actually be preferable,[41 42] and doses of only 100 mg/day have a substantial antithrombotic effect in man.[43] If to reduce gastrotoxicity still further an enteric coated preparation was used then the dose should probably not be reduced much below 80 mg/day.[44] Moreover, in the present set of trials the studies of 300-325 mg/day appeared to have yielded results that were at least as good as those yielded by 900-1500 mg/day (table VII, fig 4). This comparison is indirect and the differences noted not statistically significant; nevertheless, if aspirin is to be used prophylactically in routine medical practice there appears to be no good reason to use a dose higher than 300-325 mg/day—indeed, substantially lower doses might well be at least as effective[41-43] and would cause very little gastrotoxicity. (A main reason for choosing to test high daily doses in the original clinical trials of aspirin was simply that in 1970 tests for aspirin metabolites in urine were so crude that a high dose was needed to facilitate biochemical checks on compliance).

DIFFERENCES BETWEEN ANTIPLATELET AGENTS

Apart from aspirin the two main antiplatelet agents studied in these trials were sulphinpyrazone and aspirin combined with dipyridamole, and it would be desirable to know whether there are any clinically significant differences among the effects of these three agents on vascular disease. Three types of evidence may be considered.

Firstly, the results of individual trials may be singled out and considered in isolation from the rest. This common practice is plainly inappropriate, as by suitable selection of which trial to emphasise almost any claim might appear to be substantiated. (For example, the most promising result in any one trial was that from the GDR study of 1500 mg aspirin/day alone,[29] but it would be inappropriate to emphasise this without also emphasising the more moderate results seen in the other trials of high dose aspirin alone.)

Secondly, separate overviews may be undertaken for sulphinpyrazone *v* nil (17% (SD 8%)), for high dose aspirin *v* nil (23% (4%)), and for aspirin plus dipyridamole *v* nil (31% (5%)) and the results compared. This provides an indirect comparison of three different types of treatment. In this instance the indirect comparison suggested that aspirin plus dipyridamole may possibly be superior to aspirin alone, but the comparison was not even statistically significant (31% (SD 5%) *v* 23% (4%); 2p>0·1), and in addition it was only indirect (table VII, fig 4).

TABLE VI—*Vascular deaths recorded in trials of antiplatelet treatment (including all deaths from vascular, haemorrhagic, or unknown causes)*

	Basic data		Statistical calculations (treatment group only)	
	Allocated antiplatelet treatment	Allocated to control group	Observed No minus expected (O−E)	Variance of O−E
Completed cerebrovascular trials:				
ESPS	79/1250	106/1250	−13·5	42·8
UK-TIA	170/1621	86/814	−0·4	51·0
AICLA	25/400	12/204	0·5	7·8
CCSG	29/446	15/139	−4·5	7·4
Swedish stroke	28/253	29/252	−0·6	12·7
McMaster	21/222	31/225	−4·8	11·5
Toulouse	18/284	7/156	1·9	5·4
AITIA	10/153	13/150	−1·6	5·3
Toronto	31/143	36/147	−2·0	12·9
DCS	7/101	8/102	−0·5	3·5
Stoke	12/85	8/84	1·9	4·4
Tennessee	9/73	16/75	−3·3	5·2
German TIA	0/30	0/30	0	0
All cerebrovascular trials (excluding six still in progress (table II))	806/8689 (9%)*		−27·0 (2·1 SD from zero; 1p=0·02)	170·0 Typical odds reduction 15% (SD 7%)
Myocardial infarction trials:				
AMIS	214/2267	198/2257	7·5†	93·6
PARIS-II	97/1563	105/1565	−3·9	47·3
PARIS-I	148/1620	45/406	−6·3	28·0
Cardiff-II	97/832	122/850	−11·3	47·6
ART	65/806	82/814	−8·1	33·4
CDP-A	42/758	60/771	−8·6	23·8
GDR	12/672	26/668	−7·1	9·2
Cardiff-I	48/615	61/624	−6·1	24·9
ARIS	25/365	25/362	−0·1	11·7
GAMIS	32/317	37/309	−2·9	15·4
All myocardial infarction trials	1541/18 441 (8%)*		−47·0 (2·6 SD from zero; 1p=0·005)	334·9 Typical odds reduction 13% (SD 5%)
Unstable angina trials:				
VA (main+pilot)	16/687	27/701	−5·3	10·4
McMaster (three groups *v* one)	28/416	13/139	−2·7	7·1
All unstable angina trials	84/1943 (4%)*		−8·0 (1·9 SD from zero; 1p=0·03)	17·6 Typical odds reduction 37% (SD 19%)
All available trials	2431/29 073 (8%)*		−82·0 (3·6 SD from zero; 2p=0·0003)	522·5 Typical odds reduction 15% (SD 4%)†

*Totals for treated and control groups combined (as separate totals could not validly be compared).
†In AMIS trial randomisation produced by chance some imbalance in prognostic features recorded at entry. Unpublished calculations suggest that this would be expected to yield about 11 extra vascular deaths in treated group. Correction for it would therefore reduce observed minus expected to about 2·0 instead of 7·5 and would also reduce its variance. These corrections would change typical odds reduction for "all available trials" to 17% instead of 15%.

TABLE VII—*Direct and indirect comparisons of reductions in new vascular event rates from different antiplatelet treatments*

Trial	Aspirin 900-1500 mg daily *v* nil: Aspirin	Nil	O−E*	Variance
UK-TIA†	171/815	204/814	−16·6	72·2
AICLA†	31/198	48/204	−7·9	15·9
CCSG†	33/144	30/139	0·9	12·3
Swedish stroke	60/253	55/252	2·4	22·2
Toulouse†	12/147	17/156	−2·1	6·6
AITIA	26/153	35/150	−4·8	12·2
DCS	22/101	27/102	−2·4	9·3
German TIA	2/30	3/30	−0·5	1·2
AMIS	416/2267	458/2257	−22·0	176·3
PARIS-I†	140/810	93/406	−15·2	41·9
Cardiff-II	128/832	186/850	−27·3	63·9
CDP-A	79/758	100/771	−9·7	39·5
GDR	50/672	100/668	−25·2	33·3
GAMIS†	43/317	53/309	−5·6	20·3
McMaster†	18/139	21/139	−1·5	8·4
All high dose aspirin *v* nil	2661/14 883 (18%)		−137·5	535·5
			Typical odds reduction 23% (SD 4%)	

	Aspirin 300-325 mg daily *v* nil: Aspirin	Nil	O−E	Variance
UK-TIA†	177/806	204/814	−12·6	72·9
Cardiff-I	60/615	76/624	−7·5	30·3
VA (main+pilot)	46/687	79/701	−15·9	28·5
All medium dose aspirin *v* nil	642/4247 (15%)		−36·0	131·7
			Typical odds reduction 24% (SD 8%)	

	Sulphinpyrazone *v* nil: Sulphinpyrazone	Nil	O−E	Variance
CCSG†	48/156	30/139	6·8	14·3
ART	117/806	153/814	−17·3	56·3
ARIS	41/365	60/362	−9·7	21·8
Tennessee (excluding myocardial infarction)	21/73	25/75	−1·7	8·0
Toronto (mortality only)	34/143	38/147	−1·5	13·6
McMaster†	21/140	21/139	−0·1	9·0
All sulphinpyrazone *v* nil	609/3359 (18%)		−24·0	123·0
			Typical odds reduction 17% (SD 8%)‡	

	Aspirin+dipyridamole *v* nil: Aspirin + dipyridamole	Nil	O−E	Variance
ESPS	182/1250	264/1250	−41·0	91·7
AICLA†	30/202	48/204	−8·8	15·8
Toulouse†	12/137	17/156	−1·6	6·5
PARIS-II	189/1563	249/1565	−29·9	94·2
PARIS-I†	147/810	93/406	−12·9	42·9
All aspirin+dipyridamole *v* nil	1231/7543 (16%)		−94·2	251·1
			Typical odds reduction 31% (SD 5%)	

	Aspirin *v* sulphinpyrazone: Basic data: Aspirin	Sulphinpyrazone	Aspirin group statistics: O−E	Variance
CCSG†	33/144	48/156	−5·9	14·8
McMaster†	18/139	21/140	−1·4	8·4
ATIAIS	3/63	5/61	−1·1	1·9
Total	54/346	74/357	−8·4	25·1
			(Aspirin non-significantly better: typical odds reduction 28% (SD 17%))	

	Aspirin *v* aspirin+dipyridamole: Basic data: Aspirin	Aspirin + dipyridamole	Aspirin only statistics: O−E	Variance
ACCSG	92/442	90/448	1·6	36·2
AICLA†	31/198	30/202	0·8	13·0
Toulouse†	12/147	12/137	−0·4	5·5
PARIS-I†	140/810	147/810	−3·5	59·1
Total	275/1597	279/1597	−1·5	113·8
			(No apparent difference: typical odds reduction 1% (SD 9%))	

*O−E=Observed minus expected for treatment groups only, or for aspirin only groups.
†Trials contained more than two treatment groups; of these, only two utilised in any comparison.
‡Exclusion of one or both sulphinpyrazone trials for which only partial information available leaves typical odds reduction for sulphinpyrazone unchanged at approximately 17%.
Test for heterogeneity among four types of treatment: χ^2 on 3 degrees of freedom=3·4 (NS).

Finally, some direct randomised comparisons of the three different types of treatment were available, but, though unbiased, they were too small to be reliable. In direct comparisons of aspirin *v* sulphinpyrazone there were 54 vascular events among patients allocated aspirin and 74 among those allocated sulphinpyrazone (table VII, fig 4). This difference was not significant, but it certainly does not provide any evidence to justify the additional cost and increased frequency of treatment with sulphinpyrazone.

In trials comparing aspirin directly with aspirin plus dipyridamole a total of 275 vascular events occurred among patients allocated aspirin alone and 279 among those allocated aspirin plus dipyridamole, which again does not provide any direct evidence to justify the extra cost, side effects, and frequency of administration entailed by adding dipyridamole. Moreover, a recent review of the pharmacological effects of dipyridamole and of evidence from other clinical trials that compared aspirin directly with aspirin plus dipyridamole likewise concluded that there was no good evidence that adding dipyridamole was likely to confer any additional benefit.[45] It is important, however, not to dismiss the apparent advantage of dipyridamole in the indirect comparisons just because it was not statistically significant and not to exaggerate the strength of the negative evidence provided by the direct comparisons. There were only 275 *v* 279 vascular events in the trials of aspirin *v* aspirin plus dipyridamole, and so though these and other data[45] tend to suggest that adding dipyridamole is of little or no value, the breadth of the confidence interval (fig 4) was compatible with the suggestion that dipyridamole might somewhat increase the efficacy of aspirin but that chance just happened to obscure this benefit. What is needed is some far more extensive direct comparisons of aspirin alone (in a dose sufficient to have a strong effect on cyclo-oxygenase dependent platelet aggregation) *v* aspirin plus dipyridamole, for if dipyridamole does confer any significant additional advantage then it will be important not to overlook this.

There was, however, no good evidence from the trials reviewed that any of the antiplatelet treatments studied were more or less effective than any others. For the present the least expensive and most convenient antiplatelet treatment appears to be aspirin, perhaps at a dose no greater than (or even much less than) 300-325 mg/day. On current evidence it appears that the ideal formulation of prophylactic aspirin might be day marked calendar packs of enteric coated low dose aspirin that would virtually completely inhibit cyclo-oxygenase dependent platelet aggregation with minimal gastrotoxicity. At present such formulations are available only for clinical trials.[39]

SIZE OF PROPORTIONAL REDUCTION IN RISK

Two questions may be asked about the size of the reduction in risk that antiplatelet treatment can offer. Firstly, it may be asked what the effect would be (among people who can tolerate antiplatelet treatment without gastrotoxicity or other side effects) of actually using such treatment with 100% compliance. Secondly, it may be asked what difference would be found in trials in which half the patients were allocated active treatment and the other half control. The effect in the trials would tend to be smaller than the effect of actually using the treatment, partly because some of the patients in the active treatment group may stop the trial medication and partly because some of the controls may start to take drugs with antiplatelet effects. This would be true for non-fatal vascular events such as non-fatal stroke or non-fatal myocardial infarction that are typically of sudden onset, but it may be even more true for vascular death, as death may be preceded by some illness that results in withdrawal of active treatment. (Indeed, in some studies in this series the occurrence of a non-fatal occlusive vascular event was supposed to be a reason for stopping the trial medication.) Conversely, control patients at particular risk of death may be given antiplatelet treatment (or may treat themselves with aspirin). The degree of compliance in a study may be defined as the difference between the proportions of patients in the control and active treatment groups who are actually receiving antiplatelet treatment. On average in these trials compliance appeared to have been 0·8 or less one year after randomisation (table I), whereas in the months just before a vascular death it might well have been somewhat less.

If actual use of antiplatelet treatment could reduce the odds of suffering fatal and non-fatal vascular events by 20% and 35-40% respectively, then because of the non-compliance with active treatment (and because of the contamination of the controls) allocation to active treatment rather than control in the trials might be expected to entail differences of only about 15% and 30%, as found in this overview. Because the percentage reduction in the probability of an event is slightly less extreme than the percentage reduction in the odds of that event, these results suggest that treatment may avert about one sixth of all vascular deaths and about one third of all non-fatal vascular events (table VIII).

SIZE OF ABSOLUTE REDUCTION IN RISK

From a medical viewpoint what chiefly matters is not the proportional reduction in risk but the absolute reduction in risk, and in estimating this what matters most is not whether the proportional reduction is 15% or 20% but whether the absolute risk is high (for example, 25% dead within two years) or low (5% dead within two years). For example, over two years a typical patient with established vascular disease might have about a 6% risk of vascular death and a 6% risk of a non-fatal vascular event, in which case antiplatelet treatment might be expected to reduce these risks to about 5% and 4%. If so, then antiplatelet treatment for 100 such patients for about two years would on average avert about one vascular death and two non-fatal vascular events (table IX). But for a patient just discharged from coronary care after a myocardial infarction there is a high risk of death or reinfarction during the first few months, so that the total two year risk might be about 12% for vascular death and 9% for a non-fatal vascular event, which antiplatelet treatment might reduce to 10% and 6% (table IX). This illustrates how the absolute benefits may depend on absolute risks.

It is difficult to estimate the absolute benefits from this or any other type of treatment reliably. But if the crude estimates for the various treatments listed in table IX are approximately correct then the benefits to be expected from antiplatelet treatment in patients with some appreciable risk of occlusive disease might well be about comparable with the benefits to be expected from standard treatments, such as long term β blockade after myocardial infarction[37] or diuretic treatment for moderately hypertensive elderly patients,[46 47] and would considerably exceed the yearly benefit to be expected from the treatment of moderate hypertension in middle age.[47 48] Because for many studies only the overall results were available, without subdivision by year since randomisation (or by year since any prerandomisation vascular events), no direct evidence is provided on whether treatment should continue for one year, for several years, or indefinitely.

COMPARISON WITH OTHER ASSESSMENTS

This report has sought not an exact consensus but instead some

TABLE VIII—*Summary of main overview findings: percentage reductions (SD) in odds of various types of outcome produced by allocation to antiplatelet treatment*

Trial entry criterion	Type of outcome: Non-fatal myocardial infarction	Non-fatal stroke	Vascular death	Any vascular event
Cerebral disease (transient cerebral ischaemia or stroke)	35 (12)	22 (7)	15 (7)	22 (5)
Cardiac disease (unstable angina or myocardial infarct)	31 (5)	40 (10)	14 (5)*	26 (3)
Either disease (all cerebral or cardiac trials)	32 (5)	27 (6)	15 (4)*	25 (3)
Corresponding approximate reductions in probability of event from actual† use of treatment	⅓ Fewer with non-fatal event		⅙ Fewer vascular deaths	¼ Fewer with any vascular event

*Reduction 17% when corrected for imbalance in prognostic features in AMIS trial (In the overall results there were also slightly fewer non-vascular deaths.)
†Because of imperfect compliance allocation to treatment produced slightly less effect than actual use of treatment (but odds reductions slightly larger than probability reductions).

TABLE IX—*Crude estimates of absolute numbers of vascular events avoidable by antiplatelet treatment of 100 people for two years*

Type of subject	Agent	Events averted: Fatal	Other	Source of estimate
History of transient ischaemic attack, minor stroke, or unstable angina (with 6% dead <2 years+6% non-fatal events)	Aspirin or other antiplatelet	1	2	Present overview
Hospital discharge after recent myocardial infarction (with 12% dead <2 years + 9% non-fatal events)	Aspirin or other antiplatelet	2	3	Present overview
Hospital discharge after recent myocardial infarction (with 12% dead <2 years + 9% non-fatal events)	β Blocker	3	2	Yusuf *et al* (1985)[37]
Diastolic blood pressure 100 mm Hg, elderly	Thiazide	2	2	Amery *et al* (1985),[46] MacMahon *et al* (1986)[47]
Diastolic blood pressure 100 mm Hg, middle aged	Thiazide or β blocker	0·1	0·2	MRC (1985)[48] MacMahon *et al* (1986)[47]
No history of vascular disease in men aged:				
55-64	Aspirin	0·1*?	0·2?	15% and 30% of half death rates from coronary heart disease in Britain
65-74	Aspirin	0·2*?	0·4?	

*From these estimated reductions in coronary heart disease any adverse effect on haemorrhagic disease must be subtracted.

middle ground among a range of collaborators' views as to what possible interpretations should be emphasised. Other reviews of some of the postmyocardial infarction aspirin trials have given conclusions that are readily compatible with those in this report, though less definite because less material was reviewed.[49-52]

USE OF ASPIRIN FOR PRIMARY PREVENTION IN LOW RISK SUBJECTS?

The populations in these trials were selected for study because they had a history of disease (transient ischaemic attack, occlusive stroke, unstable angina, or myocardial infarction) that suggested a particular risk of a new occlusive vascular event; and 17% of patients suffered at least one new vascular event during the trials. In principle antiplatelet treatment might be expected to decrease the incidence of serious occlusive events but to increase the incidence of serious haemorrhagic vascular events, possibly including intracerebral haemorrhage. Unfortunately, from the information available from many of the trials it was often difficult to distinguish reliably between haemorrhagic and occlusive strokes—indeed, it was sometimes difficult to distinguish reliably between fatal stroke and fatal myocardial infarction (though the distinction between vascular and non-vascular causes of death was usually fairly clear). Hence as far as the prevention of cerebrovascular disease is concerned this overview asks merely whether treatment reduces total vascular mortality and the total incidence of non-fatal stroke without further subdivision, and in each case there was a statistically significant reduction. But though it might be reasonable to extrapolate these risk reductions to a wide range of other patients who are also at particular risk of occlusive vascular events, it might be unwise to extrapolate them to people who are not at particular risk and in whom the absolute benefit would therefore be small. For it is possible—especially in view of the results of Peto *et al* (accompanying paper)—that for apparently healthy people any small benefits might be outweighed by a small increase in cerebral or other serious haemorrhagic disease. Hence the final entry in table IX emphasises that the absolute benefits in primary prevention remain uncertain despite the results of a study of aspirin among British doctors (Peto *et al*, accompanying paper) and the early results[53] of a corresponding study of prophylactic aspirin among doctors in the United States.[40] Taken together, those two primary prevention trials show a reduction in non-fatal myocardial infarction, but they also suggest a slight increase in disabling stroke and no net reduction in vascular deaths. Thus only for patients with an appropriate history of vascular disease is there at present clear evidence that antiplatelet treatment reduces the overall incidence of fatal or disabling vascular disease.

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